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ABSTRACT

Celiac disease is an autoimmune disease that causes damage to the small intestine as a result of ingesting gluten. Approximately 1% of the U.S population has it, but individuals have a higher chance of getting the disease if they have the DQ2 gene or certain health problems. The ingestion of gluten or being on a gluten free diet can also cause additional health problems in the individual because they do not get enough vitamins and nutrients. Since a gluten free diet is not always effective, other treatments options are currently being researched including immunotherapy and modified wheat. This review will focus on genetic and health susceptibility factors in order to diagnose individuals sooner and to find more effective treatments. The implication of this new data can increase the quality of life in those affected by the disease.

KEYWORDS: celiac disease, DQ2 gene, gluten, health issues, immune response

INTRODUCTION

Celiac disease (CD) is an autoimmune disease characterized by an immune response to gluten in the small intestine.(1) CD is prevalent in 0.5-1% of the population.(1) It is associated with an individual's genetic makeup(1) and specific health problems they may have.(2) Certain individuals are more likely to develop celiac disease due to genetic variation in the major histocompatibility complex (MHC) region.(3) However, this known genetic influence is not enough to explain disease development.(3-5) Individuals with celiac disease have an increased risk of reproductive abnormalities, impaired bone health, cardiovascular and autoimmune diseases, and lymphoproliferative disorders even if they follow a strict gluten free diet (GFD), the only known effective treatment for CD.(2)

Gluten is a protein found in wheat, barely, and rye which are most often found in bread, pasta, baked goods and certain alcohols such as beer. In addition, it can be found in toothpastes, lip balms, hair and skin products, medicines, and supplements. Therefore, following a GFD can be challenging, but it allows recovery of the small intestine, specifically the villi, which absorbs nutrients. Because of this recovery, a GFD also helps lessen the severity of health problems present at diagnoses. This review will focus on the genetic influence on the disease, health issues related to both the disease and its treatment, and current research on alternative treatment methods.

GENETIC INFLUENCE

Celiac disease is a genetically susceptible disease. There are several known genes and gene combinations that increase an individual's likelihood of getting the disease. The human leukocyte antigen (HLA) complex, a version of the major histocompatibility complex (MHC), is a group of proteins that help the immune system differentiate between the body's proteins and foreign proteins.(6) The MHC class II genes are HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, and HLA-DRB1.(6) Thus far the HLA-DQA1 and HLA-DQB1 genes have been found to have the strongest effect within the MHC region on the development of the disease.(3) Individuals with CD have a 95% probability of having a DQA1 gene and a 98% probability of having a DQB1 gene(4). These account for about 23% of the heritability risk.(3)

Each MHC class II gene can have different allele variations and each variation is given a specific number.(6) The variants HLA-DQA1*05:01 or HLA-DQA1*05:05 bind to HLA-DQB1*02:01 or HLA-DQB1*02:02 to form HLA-DQ2, and the variants HLA-DQA1*03:01 or HLA-DQA1*03:02 bind to HLA-DQB1*03:02 to form HLA-DQ8.(6) Individuals with CD have a 93% probability of having a DQ2 gene.(4) In addition, individuals with the HLA molecule DQ2.5, an isoform of DQ2, are at a high risk of getting CD(7) and those who are homozygous for the haplotype DQ2 are diagnosed at a younger age.(8) Five independent variants in the MHC region (not in the HLA-DQ genes) and 57 independent single-nucleotide polymorphism (SNPs) outside the MHC region are associated with celiac disease risk.(3)

Specifically, the SNP's rs11100722 and rs4956400 from the interleukin (IL)- 15 gene were found to be associated to CD.(9) There is also a connection between the IL15RA genotype and if an individual is diagnosed as a child or an adult.(9) Not only do genes play a role in the susceptibility of an individual to CD, they also play a role in when the

individuals will get the disease. Thus, understanding the genetic background of the disease can allow for an earlier diagnosis.

HEALTH ISSUES

All CD Individuals

Since gluten exposure in CD damages the villi in their small intestine, they do not always get the amount of nutrients they need. Because of this, these individuals compared to the general population have an increase in mortality rate with malignancies, vascular disease and respiratory disease being the most common cause of death.(10, 11) This difference in mortality rate lessens as time from CD diagnosis increases.(10) In addition, individuals with CD are generally at a higher risk of getting any lymphoproliferative disease and small-intestinal lymphomas.(12) Furthermore, they are at an increased risk of myocardial infection, angina pectoris, and stroke even though they do not have the typical cardiovascular risk factors.(13) Since they do not have these typical risk factors the diagnosis and treatment of these other health problems may prove to be more difficult to determine and thus more damage to the body will happen.

Presence vs Absence of Gastrointestinal Symptoms

Individuals with CD are typically placed into two groups: those with gastrointestinal symptoms or those without gastrointestinal symptoms. It is important to study both groups as there is a delay in diagnosis between them. Individuals without gastrointestinal symptoms have a delay of 42 months from their first doctors visit to their diagnosis from biopsy compared to those who have the symptoms who usually have a delay of 2.3 months.(14) Individuals with thyroid abnormalities, other autoimmune diseases, anemia, bone mineral density loss and lower ferritin and cholesterol levels have a higher chance of having undiagnosed celiac disease and should be screened for the disease.(14, 15) These are not symptoms of CD, but they can be associated with the disease. Thus, a simple blood analysis for antibodies and/or genetic factors may give an early diagnosis. The prolonged exposure to gluten before diagnosis will cause more damage to the body than if they had been diagnosed sooner. Thus, individuals who do not have the typical gastrointestinal symptoms are more likely to have anemia (69.4% compared to 21.2%), low bone mineral density (68% compared to 41%) and abnormal thyroid-stimulating hormone (43.2% compared to 15.5%) with hypothyroidism being more common than hyperthyroidism.(14)

Gluten Free Diet

A gluten free diet is the only current treatment for CD, yet 30% of affected individuals still have symptoms(16) which can be limiting to the person's life. A study done in Italy on 13-18 year old's found 30.8% avoided restaurants most or all of the time and 7.9% avoided traveling most or all of the time.(17) Either gluten free foods and items need to be more prominent and accessible so people do not feel limited or an alternative treatment must be created that allowed CD individuals to consume gluten without harming themselves. 92.1% brought gluten-free food while traveling(17) because gluten free food can be hard to find in some locations. Having this unnecessary stress of where and what they can eat and feelings of isolation from missing out can be harmful to the individual. In fact, a GFD may cause mental or emotional problems in addition to physical problems. A study found that all CD individuals with mucosal healing had a higher risk of getting anxiety compared to CD individuals with continuous villous atrophy, and CD women with mucosal healing had a higher risk of getting depression compared to CD women who had continuous villous atrophy.(18) Their small intestine and therefore digestion was improving but avoiding the items with gluten and their vigilance to the GFD was mentally harmful.

ALTERNATIVE TREATMENTS

While a gluten free diet is the only current treatment for celiac disease, it is not always the most effective. Certain situations can make it hard for an individual to have access to gluten free food, certain foods labeled gluten free may be contaminated,(19) and individuals who do not get enough nutrients and minerals from their GFD are at a higher risk of health problems.(2) Because of this, many studies are investigating alternative treatments. A peptide-based, epitope-specific immunotherapy called Nexvax2 was used in a phase 1 study that investigated the effect of varying starting dosages and maximum dosages on villus recovery.(20) A starting dose of 3 µg and a maintenance dose of 300 µg had the least amount of drug related adverse events with only 20% of those events being graded at least moderate to severe(20) (Table 1). This drug is supposed to increase an individual's tolerance of gluten which will eventually allow them to consume gluten again without the damage it originally caused. Therefore, it will also lessen health issues associated with CD providing better quality of life to affected individuals. Participants were separated into two cohorts which may explain differences in effectiveness: cohort

1 were those who are homozygous for HLA-DQ2.5 and cohort 2 were those who are non-homozygous.(20)

Studying the immune system, specifically the characteristics that the body is having an immune response, is important in celiac disease treatments because it proves whether the treatment is effective. For instance, the presence of the antibodies anti-transglutaminase (anti-tTG) and endomysium (EMA) after ingesting gluten means the body is having an immune response. A study found individuals getting microbial transglutaminase (mTG) -modified wheat flour are less likely to have positive serum anti-tTG and EMA antibodies results and less likely to have intestinal villous atrophy because there is less or no immune response to gluten.(21) Individuals ingesting the unmodified flour had more severe bloating, nausea and abdominal pain and swelling.(21) Therefore, the modified flour seems safer than the unmodified, but approximately 25% of the individuals consuming modified flour still had disease activity following the trial(21) (Table 1). Larger and longer studies with more palatable food should be done to get a better understanding on the affect mTG modified wheat flour has on CD individuals.(21) Another study is investigating the affect oligofructose-enriched inulin, a type of prebiotic referred to as Synergy 1, on intestinal microbiota in children with CD.(22) There were only a few episodes of side effects where were fairly equal between the treatment and placebo groups.(22) The kids getting Synergy 1 had normal stools more often than the children getting the placebo (Table 1) and one child even had alleviation of CD symptoms that were present before the trial while taking Synergy 1.(22)

CONCLUSION

Celiac disease affects 0.5%-1% of the global population putting them at risk for other health issues and the only treatment is to avoid the consumption of gluten.(1) This treatment is not the most effective as it may be hard for individuals to follow this in certain situations, they may ingest contaminated food, they may continue to have symptoms, or they may feel isolated.(16, 17, 19) In addition, not everyone has the same symptoms,(14) so some people continue eating gluten even though it is damaging their intestine. It is important to study this disease because misdiagnoses, no diagnoses, or the lack of other treatments can increase chances of certain health problems and mortality. In addition, understanding the influence of specific genes on the disease can help find better treatments and allow for earlier diagnosis.(9) Additionally, broader studies should be done to find specific immunotherapy drugs that improve gluten tolerance without causing any adverse events for all individuals with celiac disease. An improved tolerance would allow individuals with CD to have more freedom in where and

what they eat and where they travel which would improve the affected individual's quality of life.

Table 1: The side effects and effectiveness of potential treatments for celiac disease

REFERENCE	TREATMENT	PARTICIPANTS	TREATMENT EFFICIENCY	PLACEBO EFFICIENCY	SIDE EFFECTS
DAVESON ET. AL[20]	Nexvax2: Starting 3ug-Maintain 300ug, Cohort 1	5	89%	84%	-Gastrointestinal disorders -Diarrhea -Nausea -Abdominal Discomfort -Gastroesophageal reflux -Nervous system disorders. -Headache -General disorders and administration sit conditions -Injection site pain
DAVESON ET. AL[20]	Nexvax2: Starting 3ug-Maintain 300ug, Cohort 2	6	90%	84%	-Gastrointestinal disorders -Diarrhea -Nausea -Abdominal pain -Abdominal discomfort -Nervous system disorders -Headache -General disorders & administration site conditions -Injection site reactions -Skin & subcutaneous tissue disorders
MARINO ET. AL[21]	mTG-modified wheat	7	71.4%	42.9%	-Intestinal villous atrophy -Nausea -Vomiting -Abdominal pain and swelling -Bloating
DRABINSKA ET. AL[22]	Oligofructose-enriched inulin	34	95%	69%	-Abdominal pain -Diarrhea

REFERENCES

1. Gujral N, Freeman HJ, Thomson AB. Celiac disease: prevalence, diagnosis, pathogenesis and treatment. World J Gastroenterol. 2012;18(42):6036-59.
2. Bathrellou E, Kontogianni MD, Panagiotakos DB. Celiac disease and non-celiac gluten or wheat sensitivity and health in later life: A review. Maturitas. 2018;112:29-33.
3. Gutierrez-Achury J, Zhernakova A, Pulit SL, Trynka G, Hunt KA, Romanos J, et al. Fine mapping in the MHC region accounts for 18% additional genetic risk for celiac disease. Nat Genet. 2015;47(6):577-8.
4. Farre C, Humbert P, Vilar P, Varea V, Aldeguer X, Carnicer J, et al. Serological Markers and HLA-DQ2 Haplotype Among First-Degree Relatives of Celiac Patients. Digestive Diseases and Sciences. 1999;44(11):2344-9.

5. Hunt KA, Zhernakova A, Turner G, Heap GA, Franke L, Bruinenberg M, et al. Newly identified genetic risk variants for celiac disease related to the immune response. Nat Genet. 2008;40(4):395-402.
6. Medicine NUSNLo. Genes 2018 [updated October 30, 2018. Explore the normal functions of human genes and the health implications of genetic changes.]. Available from: https://ghr.nlm.nih.gov/gene.
7. Sollid LM. The roles of MHC class II genes and post-translational modification in celiac disease. Immunogenetics. 2017;69(8-9):605-16.
8. Liu E, Lee HS, Aronsson CA, Hagopian WA, Koletzko S, Rewers MJ, et al. Risk of pediatric celiac disease according to HLA haplotype and country. N Engl J Med. 2014;371(1):42-9.
9. Escudero-Hernandez C, Plaza-Izurieta L, Garrote JA, Bilbao JR, Cegec, Arranz E. Association of the IL-15 and IL-15Ralpha genes with celiac disease. Cytokine. 2017;99:73-9.
10. Ludvigsson JF, Montgomery SM, Ekbom A, Brandt L, Granath F. Small-intestinal histopathology and mortality risk in celiac disease. JAMA. 2009;302(11):1171-8.
11. Peters U, Askling J, Gridley G, Ekbom A, Linet M. Causes of death in patients with celiac disease in a population-based swedish cohort. Archives of Internal Medicine. 2003;163(13):1566-72.
12. Card TR, West J, Holmes GK. Risk of malignancy in diagnosed coeliac disease: a 24-year prospective, population-based, cohort study. Aliment Pharmacol Ther. 2004;20(7):769-75.
13. Ludvigsson JF, James S, Askling J, Stenestrand U, Ingelsson E. Nationwide cohort study of risk of ischemic heart disease in patients with celiac disease. Circulation. 2011;123(5):483-90.
14. Paez MA, Gramelspacher AM, Sinacore J, Winterfield L, Venu M. Delay in Diagnosis of Celiac Disease in Patients Without Gastrointestinal Complaints. Am J Med. 2017;130(11):1318-23.
15. Choung RS, Larson SA, Khaleghi S, Rubio-Tapia A, Ovsyannikova IG, King KS, et al. Prevalence and Morbidity of Undiagnosed Celiac Disease From a Community-Based Study. Gastroenterology. 2017;152(4):830-9 e5.
16. Board CDFsMA. Celiac Disease Foundation [Available from: https://celiac.org/.
17. Altobelli E, Paduano R, Gentile T, Caloisi C, Marziliano C, Necozione S, et al. Health-related quality of life in children and adolescents with celiac disease: survey of a population from central Italy. Health and Quality of Life Outcomes. 2013;11(1):204.

18. Ludvigsson JF, Lebwohl B, Chen Q, Broms G, Wolf RL, Green PHR, et al. Anxiety after coeliac disease diagnosis predicts mucosal healing: a population-based study. Aliment Pharmacol Ther. 2018.
19. Bascunan KA, Vespa MC, Araya M. Celiac disease: understanding the gluten-free diet. Eur J Nutr. 2017;56(2):449-59.
20. Daveson AJM, Ee HC, Andrews JM, King T, Goldstein KE, Dzuris JL, et al. Epitope-Specific Immunotherapy Targeting CD4-Positive T Cells in Celiac Disease: Safety, Pharmacokinetics, and Effects on Intestinal Histology and Plasma Cytokines with Escalating Dose Regimens of Nexvax2 in a Randomized, Double-Blind, Placebo-Controlled Phase 1 Study. EBioMedicine. 2017;26:78-90.
21. Marino M, Casale R, Borghini R, Di Nardi S, Donato G, Angeloni A, et al. The effects of modified versus unmodified wheat gluten administration in patients with celiac disease. Int Immunopharmacol. 2017;47:1-8.
22. Drabinska N, Jarocka-Cyrta E, Markiewicz LH, Krupa-Kozak U. The Effect of Oligofructose-Enriched Inulin on Faecal Bacterial Counts and Microbiota-Associated Characteristics in Celiac Disease Children Following a Gluten-Free Diet: Results of a Randomized, Placebo-Controlled Trial. Nutrients. 2018;10(2).

Reynolds, L. (2019). Genetic and Health Influence on Celiac Disease and Future Treatment Options. *D.U. Quark*, 3(2). Retrieved from https://dsc.duq.edu/duquark/vol3/iss2/2